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Avoiding mixtures of different mitochondria leads to effective mitochondrial replacement

Scientists identify specific strategies including egg freezing for moving to the clinic

New York, NY (May 19, 2016) – Scientists at The New York Stem Cell Foundation (NYSCF) Research Institute discovered an important biological phenomenon in human cells that will help scientists and clinicians design safer treatments to prevent mitochondrial diseases. NYSCF first pioneered a technique, mitochondrial replacement therapy (MRT), in 2012 to prevent inheritance of these devastating and debilitating diseases. Now, scientists at the NYSCF Research Institute and Columbia University are working to hone this technique and understand the biological processes that would impact patients as this process is brought into clinical trials.

Mitochondria function as cellular batteries. People born with malfunctioning mitochondria experience a spectrum of symptoms potentially resulting in childhood death, including stunted development, neurological disorders, heart disorders, and stomach and digestive problems. Published in *Cell Stem Cell*, Dr. Dieter Egli, Senior Research Fellow at the NYSCF Research Institute and an assistant professor at Columbia University College of Physicians and Surgeons, and his colleagues transferred nuclear DNA into cells from different donors to understand more about MRT and its clinical applications. Dr. Egli explained, "This is one more step towards the therapeutic application of mitochondrial replacement and informs us how MRT is best conducted clinically."

Working in close collaboration with Drs. Michio Hirano and Mark Sauer and their teams at Columbia University Medical Center, this research continues to lay the groundwork for future clinical trials by showing that mitochondria from an individual can successfully be replaced with mitochondria from any unrelated donor. They found that nuclear DNA and mitochondrial DNA from different individuals are compatible. This alleviates a common concern regarding MRT— that replacing diseased mitochondria with healthy mitochondria from a different individual may prove incompatible—and brings a critical piece of information requisite to translating this innovative preventive treatment to patients waiting to build families.

"For women who are affected with these diseases, this work brings hope that they will have access to therapies that will allow them to have healthy children. Since our initial work with MRT, we have advocated for the FDA to permit clinical trials that enable women to prevent their children from inheriting mitochondrial diseases. I hope this research provides further evidence to the FDA to approve this work for clinical application," explained Susan L. Solomon, Co-Founder and CEO of The New York Stem Cell Foundation.

The researchers made an important discovery, finding that during the transfer of nuclear DNA into donor cells with healthy mitochondria there may be some carry-over of mitochondria from the donor individual's cells. The resulting cells may contain two different types of mitochondria. Sometimes the carried-over mitochondria decrease in quantity and becomes barely detectable or are eliminated altogether as the cells grow and divide. However, in rare circumstances, these transferred mitochondria increase in quantity as cells divide, negating the replacement of the affected mitochondria.

To combat the potential adverse outcome Dr. Egli, a NYSCF – Robertson Stem Cell Investigator suggests, "In order to prevent the transmission of mitochondrial diseases, we need to avoid competitive situations between mitochondrial genotypes of the parent and of the mitochondrial donor. The co-existence of the two-mitochondrial types within one cell must be avoided through minimizing or even eliminating carry-over during transfer."

Another important discovery from this work revealed that scientists can freeze the eggs that contain the nuclear DNA for mitochondrial replacement. A key insight allowing doctors to avoiding having to sync ovulation between the patient and donor for effective treatment when MRT is brought to clinical trials.

Dr. Mitsutoshi Yamada, formerly a Postdoctoral Fellow at the New York Stem Cell Foundation Research Institute, was the first author on the study and is now at Keio University School of Medicine in Japan.

About the New York Stem Cell Foundation

The New York Stem Cell Foundation (NYSCF) is an independent organization founded in 2005 to accelerate cures and better treatments for patients through stem cell research. NYSCF employs over 45 researchers at the NYSCF Research Institute, located in New York, and is an acknowledged world leader in stem cell research and in developing pioneering stem cell technologies, including the NYSCF Global Stem Cell Array™. Additionally, NYSCF supports another 75 researchers at other leading institutions worldwide through its Innovator Programs, including the NYSCF – Druckenmiller Fellowships and the NYSCF – Robertson Investigator Awards. NYSCF focuses on translational research in a model designed to overcome the barriers that slow discovery and replaces silos with collaboration. For more information, visit www.nyscf.org